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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/318,870	05/26/1999	ANDREW H. SEGAL	3378/80489	2018

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/318,870	SEGAL, ANDREW H.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,13,14,17-20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 13-14, 17-20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 09/09/05 is acknowledged.

Claims 1-8, 13-14, 17-20 and 22-25 are pending.

In view of the amendment, filed on 09/09/05 the following rejection remains:

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

3. Claims 1-8, 13-14, 17-20 and 22-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hiserodt et al. (US Patent 6,277,368) in view of the Known fact disclosed in the Specification on pages 52-54 and 66 – 68 set forth in the previous Office Action, mailed on 03/11/05.

Applicant's arguments, filed 09/09/05 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) US Patent '368 does not teach a composition comprising a cell and an engineered cytokine, where the composition is substantially free of the cells that have been genetically modified to produce cytokine, (ii) the disclosure on pages 52-54 of the instant specification is not a known fact but a portion of the disclosure of the invention.

Applicants have traversed the primary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC 103 not under 35 USC 102. Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would

collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

In the instant case, US Patent '368 teaches a method of stimulating an immune response in a mammal, including to selected antigen, comprising administering a vaccines comprising a primary tumor cells and cytokine-secreting cells (see entire document, Abstract in particular). It is noted that "cytokine-coated cells" of the present invention are obtained by mixing cell that already express an antigen, a tumor cell antigen for example, with engineered cytokines that can become membrane-bound (see page 79 lines 9-25 of the instant Specification in particular). US Patent '368 teaches that cytokines secreted by said cytokine-secreting cells are exogenous to primary tumor cells (see column 7, lines 25-40 in particular). US Patent '368 teaches that cytokine is a GM-CSF, that is a ligand for GM-CSF receptor (see column 7, lines 31, or column 10, lines 52-65 in particular). US Patent '368 teaches that said cytokines can be membrane-bound capable of potentiating an immunological response against the tumor-associated antigen (column 15, lines 36-45 in particular). US Patent '368 teaches a immunogenic composition comprising 2 population of cells: first population is tumor cells i.e. specific antigen expressing cells and second population is the cytokine-producing cells (see column 15, line 35-40 and claim 9 in particular). Cytokines secreted by said second cytokine-secreting cells would be exogenous cytokines that are produced outside of first population of antigen expressing cells, that will become "cytokine-coated cells", wherein said cytokine of said cytokine-coated cells is exogenous to said antigen expressing cell. In other words US Patent '368 teaches the administering an immunogenic composition comprising cell comprising antigen that are admixed with cytokine, produced by cytokine-secreting cells. Moreover, US Patent '368 teaches that it is preferable that cytokine attached to the cell membrane to keep it in the vicinity of bystander tumor antigen comprised in the vaccine (see column 16, lines 28-35 in particular). US Patent '368 teaches that when particular cytokines have potent immunostimulatory activity but do not occur naturally in a membrane-bound form, it is possible to engineer membrane-bound forms , with a high degree of lipophyllicity (see column 16, line 50-65 in particular). US Patent '368 teaches that cytokines can be engineered to become stable associated with the plasma membrane (see column 16, lines 50-65 in particular). US Patent '368 teaches that said vaccine composition can be attenuated (see overlapping columns 23 and 24 in particular). US Patent '368 teaches the advantage of using a membrane-bound cytokines over soluble cytokines to increase an immune response to an antigen comprises by the cell (see column 16, lines 40-50 in particular).

US Patent '368 does not explicitly teaches engineered cytokine wherein said engineered cytokine comprises a cytokine and a moiety heterolous to said cytokine wherein said moiety binds to said cell and wherein said composition being substantially free of cells that have been genetically modified to produce cytokine, as claimed in claim 1-2, 13 or 15 or specific opsonin-enhanced cells as recited in claims 3-8 and 20.

The Known fact disclosed in the Specification on pages 52-54 and 66 – 68 teaches that it is conventional and within the skill of the art to produce : (i) an opsonin-enhanced cells, wherein

opsonin of said cells is mannose binding protein or alph' chain of C3b to allow more efficient binding, engulfment and internalization of the antigen; (ii) an engineered cytokine by attaching the lipid , e.g. a lond-chain fatty acid, for example palmitate or GPI moiety to said cytokine to permit a complex to become stable associated with plasma membrane. In other words, at the time the invention was made one skill in the art would know how to produced an engineered membrane-bound form of cytokine, comprising hetorologoues moiety wherein said moiety binds to the cell.

With regards to Applicant's comments that the disclosure on pages 52-54 of the instant specification is not a known fact but a portion of the disclosure of the invention. Applicant's attention is respectively drawn to pages 54 and 66 of the instant specification in particular. The Specification disclosed that " moieties through which molecules can be stably bound to cell include crosslinking moieties, transmembrane sequence and lipid moieties. The preparation of proteins containing these sequences or moieties **is well-known to one skill in the art**" The Specification further teaches " . On page 66 the Specification disclosed several prior art references teaching that the attachment of a lipid, e.g. long-chain fatty acid to a polypeptide permit the complex to become stably associated with the plasma membrane **when the complex is admixed with the cell** (emphasis added). Thus, it is the examiner position that the disclosure of the instant specification on pages 52-54 is indeed the prior art knowledge that Applicant, as well as skilled in the art used to engineered polypeptide, for example, cytokine bound to the cell surface.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of the Known fact disclosed in the Specification on pages 52-54 and 66 – 68 to those of US Patent '368 to obtain a claimed method of stimulating a mammal to a selected antigen, comprising administering composition comprising an opsonin-enhanced cells and engineered cytokine comprising a lipid or GPI moiety or palmitate.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because engineered cytokine wherein lipid , e.g. a lond-chain fatty acid, for example palmitate or GPI moiety is attached to said cytokine permits said complex to become stable associated with plasma membrane of the cell and an opsonin-enhanced of said cells, allows more efficient binding, engulfment and internalization of said engineered cytokine into said cell as taught by the known fact disclosed in the Specification on pages 52-54 and 66-68. Thus the engineered cytokines that will become membrine-bound can be obtained that can be further used instead of cytokine-producing cells in the method taught by US Patent '368, because US Patent '368 teach the advantage of using a membrane-bound cytokines over soluble cytokines to increase an immune response to an antigen comprises by the cell. Further, it would be immediately obvious to one of ordinary skill in the art that in case engineered cytokines that become membrine-bound are used in a composition, instead of instead of cytokine-producing cells in the method taught by US Patent '368, then said composition would be substantially free of cells that have been genetically modified to produce cytokine.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The following new grounds of rejection are necessitated by the amendment filed 09/09/05.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 3, 4-8, 13, 14, 17-20, 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 13 are indefinite and ambiguous in the recitation of "said composition being substantially free of cells ". The characteristics and metes and bounds of "substantially free" are unclear and indefinite . The Specification provide no guidance what composition is considered to be a "substantially free" composition?

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8, 13-14, 17-20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

" ...said composition being substantially free of the cells that have been genetically modified to produce cytokine" claimed in claims 1 and 13; (ii) " ...wherein said cytokine-coated cells has not been genetically modified to produce cytokine" represent a departure from the specification and the claims as originally filed and applicant has not pointed out where the support come from. The specification and the claims as originally field only support " composition comprising a cell comprising said antigen admixed with an engineered cytokine wherein said engineered cytokine comprises a cytokine and moiety heterologous to said cytokine".

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 571/273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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